Annals of Clinical and Analytical Medicine
Original Research

Evaluation of the relationship between helicobacter pylori infection diagnosed by gastric biopsy and benign prostatic hyperplasia and prostate cancer

Evaluation of the relationship between helicobacter pylori infection and prostate disease

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Abstract
Aim: It is believed that the systemic inflammation caused by the Helicobacter pylori (HP) bacterium's cag-A and vac-A virulence factors, along with the effects of apoptosis and local growth factors on an atherosclerotic background, may play a role in the development of chronic prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa) in the prostate gland. This study aimed to evaluate the relationship between HP infection diagnosed through the invasive diagnostic method of gastric biopsy and BPH and prostate cancer.
Material and Methods: A total of 140 patients with dyspepsia, who underwent transurethral prostatectomy (TUR-P) due to coexisting benign prostatic hyperplasia or prostate cancer, as well as patients diagnosed with BPH and/or PCa who did not undergo TUR-P, were retrospectively included in our study. A control group of 100 patients with similar dyspeptic complaints but without prostate disease in the same age group was formed. Gastric biopsy results of both groups were evaluated for HP, intestinal metaplasia, and gastric atrophy.
Results: Our study showed no statistically significant differences in the distribution of HP infection, intestinal metaplasia, and gastric atrophy among patients with dyspepsia based on the presence of BPH or prostate cancer ($p>0.05$).
Discussion: Although it is hypothesized that HP may have an etiological role in BPH and prostate cancer, it cannot be definitively stated that it directly contributes to the etiology.

Keywords
Helicobacter Pylori, Benign Prostatic Hyperplasia, Prostate Cancer, Inflammation, Dyspepsia

DOI: 10.4328/ACAM.21857 Received: 2023-08-10 Accepted: 2023-09-12 Published Online: 2023-09-18 Printed: 2023-12-01 Ann Clin Anal Med 2023;14(12):1125-1129
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This study was approved by the Clinical Research Ethics Committee of Giresun Training and Research Hospital (Date: 2023-03-13, No: 05)

Introduction

Helicobacter pylori (Hp) is a spiral-shaped, gram-negative bacterium approximately 3.5 microns long and 0.5 microns wide [1]. Age, ethnicity, gender, geography, and socioeconomic status are factors that influence the incidence and prevalence of Hp infection. Hp prevalence is higher in developing countries and lower in developed countries. Additionally, there is variation in Hp prevalence between urban and rural populations within the same country. The worldwide prevalence of Hp is over 50% [2]. In recent years, the increasing development of resistance to first-line antibiotics has made biopsy-based diagnosis necessary even in regions where Hp is endemic, regardless of the presence of alarming symptoms [3].

Hp plays a role in the pathogenesis of several gastrointestinal-related diseases, including Functional Dyspepsia (Non-Ulcer Dyspepsia), Gastroesophageal Reflux Disease (GERD), Gastritis, Peptic Ulcer, Gastric Cancer, and Gastric Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma [4]. Hp is also involved in the etiology of extra-gastrointestinal pathologies originating from vascular, respiratory, liver, skin, and renal sources. Direct exposure to the bacterium and pathogenic antigens initiates inflammation, leading to cytokine release, which explains its role in the development of extra-gastrointestinal diseases. Studies suggest that Hp may affect the prostate gland, potentially contributing to chronic inflammation and neoplastic diseases in the prostate gland [5]. A study conducted in the United States in 2013 found a positive correlation between Hp infection and low androgen production in the male population [6].

Hp's major virulence factors are the vac-A (vacuolating cytotoxin gene A) and cag-A (cytotoxin-associated gene A) antigens. The cag-A antigen, being more virulent than vac-A, is responsible for Hp's development of local and systemic inflammatory responses. The cag-A gene induces the production of inflammatory mediators such as TNF-alpha, IFN-gamma, IL-1beta, IL-6, IL-8, and IL-10, leading to chronic inflammation and systemic inflammatory responses. It is believed that this systemic inflammation, along with apoptosis and the effects of local growth factors, may contribute to the development of atherosclerotic conditions, potentially playing a role in chronic prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa) in the prostate gland [7].

Reviewing the literature, it can be noted that studies have been conducted to evaluate the relationship between BPH, prostate cancer, and Hp infection based on this mechanism. In this context, in our country, where Hp positivity is endemic in dyspeptic patients, we aimed to conduct a study evaluating the relationship between Hp infection diagnosed by invasive gastric biopsy diagnostic method and BPH and prostate cancer.

Material and Methods

Approval for our study was obtained from the Giresun Training and Research Hospital Clinical Research Ethics Committee (Decision No. 05 dated March 13, 2023).

Patients who presented to the departments of Internal Medicine and Gastroenterology between January 03, 2022, and December 30, 2022, and underwent transurethral prostatectomy (TUR-P) due to benign prostatic hyperplasia and/or prostate cancer accompanied by dyspepsia, as well as patients diagnosed with benign prostatic hyperplasia and/or prostate cancer accompanied by dyspepsia who did not undergo TUR-P, were retrospectively included in the study. Patients with acute and chronic prostatitis were not included. Patients underwent upper gastrointestinal endoscopy and gastric biopsy procedures. Gastric biopsies were evaluated for the presence of accompanying Hp infection, intestinal metaplasia, and gastric atrophy. The results of gastric biopsy were evaluated in a total of 140 patients meeting these criteria and 100 patients (control group) with similar dyspeptic complaints but without prostate disease in the same age group.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 26.0 Statistics software. The normal distribution of numerical variables of the patients was assessed by examining the skewness values. It was observed that platelet, lymphocyte, hemoglobin, potassium, C-reactive protein (CRP), hematocrit, and mean corpuscular volume (MCV) values complied with the rules of normal distribution, with reference values taken within ±1.5. The Chi-square test was used to compare age and pathological findings based on the presence of prostate disease and the implementation of transurethral prostatectomy. An independent Sample T-test or Mann-Whitney U test was used to compare age, total PSA, and laboratory parameters based on the presence of prostate disease and the implementation of TUR-P. Pearson's or Spearman's correlation tests were used to examine the relationships between the implementation of TUR-P and age, total PSA, laboratory, and pathological findings. The correlation coefficient was considered low for values between 0.00-0.30, moderate for values between 0.30-0.70, and high for values between 0.70-1.00. The significance levels for all analyses were conducted considering p-values of 0.05 and 0.01.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 240 patients with dyspeptic symptoms were included in our study. Among them, 41.7% of the patients did not have prostate disease, while 58.3% had either benign prostatic hyperplasia (BPH) or prostate cancer (PCa). The comparison of patients' age, total PSA, and gastric pathology findings based on the presence of prostate disease is shown in Table 1.

Among patients with dyspeptic symptoms and no prostate disease, 73% were aged 70 or younger, while 27% were aged 70 or older. Among patients with dyspeptic symptoms and prostate disease, 62.9% were aged 70 or younger, and 27% were aged 70 or older. The mean age of patients without prostate disease was 63.67 years, while the mean age of patients with prostate disease was 69.76 years. According to these findings, there was no significant difference in age distribution based on the presence of prostate disease in patients with dyspeptic symptoms ($p>0.05$). However, a significant difference was observed in the mean age between patients with dyspeptic symptoms and prostate disease ($p<0.05$).

Out of the prostate patients, 87.9% (123 patients) had BPH, 12.1% (17 patients) underwent TUR-P, and 25% (35 patients) had co-existing prostate cancer. The mean total PSA value among these patients was 1.92.

Table 1. Comparison of Patients' Age, Total PSA, and Gastric Pathology Findings According to the Presence of Prostate Disease.

Variables		No prostate disease (n: 100)		Presence of prostate disease (n: 140)		p
		Number	%	Number	%	
Age	Under 70 years	73	73	88	62,9	0,131
	Over 70 years	27	27	52	37,1	
Bph	Negative	0	0	17	12,1	-
	Positive	0	0	123	87,9	
Hp	Negative	59	59	73	52,1	0,357
	Positive	41	41	67	47,9	
Intestinal metaplasia	Negative	68	68	102	72,9	0,524
	Positive	32	32	38	27,1	
Gastric atrophy	Negative	81	81	108	77,1	0,499
	Positive	19	19	32	22,9	
Tur-p	No	0	0	123	87,9	-
	Exist	0	0	17	12,1	
PCa	No	0	0	105	75	-
	Exist	0	0	35	25	
		Mean ± S.D. Med. (Min.-Max.)		Mean ± S.D. Med. (Min.-Max.)		
Total PSA		-		1,92±2,66 1,10 (0,01-19)		-
Aget		63,67±8,27 64 (46-81)		66,79±8,46 67 (50-96)		0,005*

Table 2. Comparison of Patients' Laboratory Parameters According to the Presence of Prostate Disease.

Laboratory parameters	No prostate disease (n: 100)	Presence of prostate disease (n: 140)	p
	Mean ± S.D. Med. (Min.-Max.)	Mean ± S.D. Med. (Min.-Max.)	
Platelet[t]	259,62±70,46 258,00 (117-568)	240,14±83,98 223,00 (80-665)	0,558
Lymphocyte[t]	1,87±0,54 1,80 (1,00-3,60)	2,08±0,74 2,04 (0,28-5,33)	0,021*
Wbc (White blood cell)[z]	7,11±1,96 6,85 (3,90-14,38)	7,26±2,42 6,86 (3,74-17,06)	0,934
Hemoglobin[t]	12,94±2,32 13,85 (6,26-16,20)	13,61±2,08 14,20 (7,60-17,50)	0,021*
Glucose[z]	106,85±37,60 97,50 (65-338)	120,29±50,09 106,00 (63-462)	0,001**
Urea[z]	32,88±10,36 30,00 (20-59)	41,59±24,48 36,00 (19-198)	0,067
Creatinine[z]	,93±0,024 0,90 (0,60-2,73)	,98±0,41 0,90 (0,30-3,50)	0,684
ALT (alanine aminotransferase)[z]	18,37±11,04 15,00 (6-84,00)	20,85±39,27 16,00 (5,00-470,00)	0,862
AST (aspartate aminotransferase)[z]	20,72±6,20 20,00 (5,00-37,00)	26,20±61,30 19,00 (9,00-723,00)	0,376
Sodium[z]	140,30±2,92 141,00 (132-145)	139,93±3,28 140,00 (126-148)	0,238
Potassium[t]	4,54±0,42 4,50 (3,60-5,30)	4,50±0,47 4,50 (3,10-6,30)	0,513
Calcium[z]	9,61±0,44 9,50 (8,80-10,80)	9,50±0,70 9,60 (5,60-10,60)	0,78

Table 3. Comparison of Age, Total PSA, Presence of Prostate Cancer, and Gastric Pathology Findings in Patients with and without Tur-p.

Variables		Transurethral Prostatectomy not Performed (n:123)		Transurethral Prostatectomy Performed (n:17)		p
		Number	%	Number	%	
Age	Under 70 years	81	65,9	7	41,2	0,088
	Over 70 years	42	34,1	10	58,8	
Hp	Negative	64	52	9	52,9	0,944
	Positive	59	48	8	47,1	
Intestinal metaplasia	Negative	89	72,4	13	76,5	0,932
	Positive	34	27,6	4	23,5	
Gastric atrophy	Negative	93	75,6	15	88,2	0,506
	Positive	30	24,4	2	11,8	
PCa	No	97	78,9	8	47,1	0,011*
	Exist	26	21,1	9	52,9	
		Mean ± S.D. Med. (Min.-Max.)		Mean ± S.D. Med. (Min.-Max.)		
Total psaz		2,00±2,67 1,25 (0,01-19)		1,35±2,61 0,02 (0,01-8,4)		0,01**
Aget		66,32±8,51 66 (50-96)		70,24±7,43 73 (54-80)		0,073

Among patients without prostate disease, 41% (41 patients) had Hp infection, 32% (32 patients) had intestinal metaplasia, and 19% (19 patients) had gastric atrophy. Among patients with prostate disease, 47.9% (67 patients) had Hp infection, 27.3% (38 patients) had intestinal metaplasia, and 23.5% (32 patients) had gastric atrophy. Based on these findings, no significant difference was observed in the distribution of Hp infection, intestinal metaplasia, and gastric atrophy based on the presence of prostate disease in patients with dyspeptic symptoms (p>0.05).

Table 2 presents the comparison of laboratory parameters among patients based on the presence of prostate disease.

There was no significant difference in platelet, WBC, urea, creatinine, ALT, AST, sodium, potassium, and calcium values based on the presence of prostate disease (p>0.05). However, a significant difference was observed in lymphocyte, hemoglobin, and glucose values (p<0.05). The mean lymphocyte value in patients without prostate disease was 1870/mm3, hemoglobin 12.9 g/dL, and glucose 97.50 mg/dL. In patients with prostate disease, the mean lymphocyte value was 2080/mm3, hemoglobin 13.6 g/dL, and glucose 106 mg/dL. According to these results, patients with prostate disease had significantly higher mean values of lymphocytes, hemoglobin, and glucose compared to those without prostate disease (p-values for lymphocytes, hemoglobin, and glucose were 0.021, 0.021, and 0.001, respectively).

A total of 140 patients with dyspeptic symptoms and prostate disease were included in our study as the case group. It was found that 87.9% of them did not undergo TUR-P, while 12.1% underwent the procedure. The comparison of age, TSH, PSA, and pathology findings between patients who underwent TUR-P and those who did not is presented in Table 3.

Among patients who did not undergo TUR-P, 65.9% were aged 70 or younger, while 34.1% were aged 70 or older. Among patients who underwent TUR-P, 41.2% were aged 70 or younger, and 58.8% were aged 70 or older. The mean age of patients who did not undergo TUR-P was 66.32, while the mean age of patients who underwent TUR-P was 70.24. According to these findings, no significant difference was observed in age distribution and mean age between patients with dyspeptic symptoms and prostate disease based on the implementation of TUR-P (p>0.05).

Among patients who did not undergo TUR-P, 48% (59 patients) had Hp infection, 27.6% (34 patients) had intestinal metaplasia, 24.4% (30 patients) had gastric atrophy, and 21.1% (26 patients) had co-existing prostate cancer. Among patients who underwent TUR-P, 47.1% (8 patients) had Hp infection, 23.5% (4 patients) had intestinal metaplasia, 11.8% (2 patients) had gastric atrophy, and 52.9% (9 patients) had prostate cancer. The mean total PSA value in patients who did not undergo TUR-P was 1.25, while it was 0.02 in patients who underwent TUR-P. Based on these results, no significant difference was observed in the distribution of Hp infection, intestinal metaplasia, and gastric atrophy, and no significant difference was observed in the distribution of prostate cancer and total PSA based on the implementation of TUR-P in patients with dyspeptic symptoms and prostate disease (p>0.05). However, the presence of prostate cancer was found to be significantly higher in patients who underwent TUR-P (p:0.011). Additionally, the total PSA value was significantly lower in patients who underwent TUR-P compared to those who did not (p:0.01).

There was no significant difference in platelet, lymphocyte, WBC, hemoglobin, glucose, urea, creatinine, ALT, AST, sodium, potassium, calcium, neutrophil, and ferritin values based on the implementation of TUR-P (p>0.05).

Discussion

In our study, no statistically significant difference was observed in the distribution of Hp infection, intestinal metaplasia, and gastric atrophy based on the presence of BPH or prostate cancer in patients with dyspeptic symptoms (p>0.05). Additionally, no significant difference was found in the distribution and mean values of age, Hp infection, intestinal metaplasia and gastric atrophy among dyspeptic patients with or without TUR-P (p>0.05).

Upon reviewing the literature, it was observed that there were no studies conducted on the population of dyspeptic patients specifically evaluating the relationship between BPH/prostate cancer and Hp infection, intestinal metaplasia, and gastric atrophy based on gastric biopsies obtained during upper gastrointestinal endoscopy. Thus, our study is considered the first to evaluate these relationships.

When reviewing the literature regarding the assessment of the relationship between Hp infection and BPH/prostate cancer, it was found that the evaluation method typically involves molecular tests (real-time PCR) and/or immunohistochemical methods to assess the presence of Hp in the prostate tissue obtained from patients undergoing TUR-P or open prostatectomy.

In a study conducted at Istanbul Fatih Sultan Mehmet Training and Research Hospital, 113 patients who underwent TUR-P due to BPH between June 2012 and June 2013 were included. The presence of Hp was evaluated using real-time PCR in prostate tissue samples. In this study, Hp was detected in 1.8% of cases (2 patients), and chronic prostatitis was observed in 58.4% of cases (66 patients). The study concluded that the molecular detection of Hp in prostate tissue may suggest that Hp could contribute to the development of chronic prostatitis and BPH through inducing inflammation, thus requiring further investigations [7].

Another study in Iran included a total of 160 patients who underwent TUR-P or open prostatectomy due to BPH. Real-time PCR was used to assess the presence of Hp DNA in prostate tissues, and Hp was detected in 1.87% of cases (3 patients) [8].

At Sultan Qaboos University, Al-Marhoon et al. conducted a study with 100 patients, of whom 78% had BPH and 19% had prostate cancer. Immunohistochemical methods were used to assess the presence of Hp in prostate tissues, and Hp was not detected. However, using real-time PCR, Hp was detected in 5 patients. The Hp antigen test in the stool was also positive in these 5 patients. Based on similar studies, no statistically significant difference was observed between the presence of Hp DNA in prostate tissue and the development of BPH and prostate cancer (p>0.05). The absence of a direct statistically significant relationship could be attributed to the lack of favorable environmental conditions for Hp to survive in the prostate gland [8].

In a study conducted by Christopoulos and Stamatiou in Greece, they evaluated the relationship between Hp infection and prostate diseases, including chronic prostatitis and BPH leading to prostate cancer, from 1960 to 2010 using PubMed and Medline databases. They found a hypothesis-level association between Hp infection and the development of prostate cancer in the context of chronic prostatitis and BPH. However, their study did not provide statistically significant and experimentally based evidence for this association [9].

Conclusion

These studies that rely on the detection of Hp DNA in prostate tissue using molecular methods have certain limitations, such as the high cost of the molecular technique and the inclusion of a small number of patients, which may limit their generalizability. Further research with larger sample sizes and more comprehensive evaluation methods is warranted to gain a better understanding of the potential relationship between Hp infection and BPH/prostate cancer. Departments of Internal Medicine, Gastroenterology and Urology should conduct multidisciplinary studies in this field.

Limitation

In our study, we did not detect the presence of Hp in the prostate tissues of patients who underwent TUR-P using molecular or immunohistochemical methods. However, it is important to note that our study had some limitations, including the lack of molecular testing for Hp infection and the relatively small sample size of 140 patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content

including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding: *None*

Conflict of interest
The authors declare no conflict of interest.

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How to cite this article:
Ersin Kuloğlu, Ahmet Cumhur Dülger. *Evaluation of the relationship between helicobacter pylori infection diagnosed by gastric biopsy and benign prostatic hyperplasia and prostate cancer. Ann Clin Anal Med 2023;14(12):1125-1129*

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